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Original Article

Impact of Sumac on postprandial high-fat oxidative stress

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ABSTRACT

Background and Objective: High-fat diet causes a sudden increase in blood lipids and oxidative stress after each meal, which can affect the trigger mechanisms of atherosclerosis and cause some acute changes in the function of vessels' endothelial cells. With respect to the antioxidant properties of Sumac (*Rhus coriaria*), the present research was conducted to determine the effect of taking Sumac along with food on some atherosclerosis risk factors resulting from high-fat diet in hypercholesterolemic rabbits.

Methodology: In this experimental study, 24 New Zealand rabbits were randomly designated into three eight-member groups as follows: normal diet, high-cholesterol diet (1%), high-cholesterol diet and Sumac powder 2%. Oxidative stress factors and those influencing atherosclerosis or arterial function including glucose, total cholesterol (TC), triglyceride (TG), Apo lipoprotein B (Apo B), low-density lipoprotein (LDL-C), nitrate, nitrite, fibrinogen and factor VII, and also liver enzymes (ALT, AST) were measured and compared in each group.

Results: High cholesterol diet significantly increased total cholesterol, fibrinogen, triglycerides, glucose, nitrate, LDL-C and the liver enzymes ALT and AST ($p < 0.05$). Use of powdered Sumac revealed a significant decrease in the blood levels of glucose (30.15%), LDL-C (58.17%), total cholesterol (29.5%), ALT (17.46%), AST (20.55%) and fibrinogen (17.92%) compared to the high-cholesterol diet group ($p < 0.05$), but did not induce any significant changes on triglyceride (TG), factor VII, nitrite, nitrate and ApoB ($p > 0.05$).

Conclusions: This study demonstrates the protective effect of consuming Sumac with food on some risk factors of atherosclerosis and oxidative stress (glucose, LDL-C, total cholesterol and fibrinogen) and also liver enzymes induced by high fat food.

KEY WORDS: Atherosclerosis, Traditional Medicine, Lipid Metabolism.

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INTRODUCTION

Postprandial increase in oxidative stress induced by food intake in the body is associated with increased glucose concentration, triglyceride and oxidative pressures.[1-3] Damage to cellular structures including proteins, carbohydrates and fats can be due to the increased oxidative activity during this stage.[1,3] High-fat diet can affect the trigger mechanisms of atherosclerosis, because it causes acute changes in vessel's endothelial cells.[1-3] Antioxidants may be useful at the time of postprandial oxidative stress through preventing the vulnerability of organism. Lipid or carbohydrate-

rich food will be the target of oxidative changes after absorption or presenting in peroxidative form in foodstuff.[3,4] Sumac contains antioxidants, flavonoids, and hydrolysable tannins which have anticancer, anti-tumor and hypoglycemic properties.[5-10] Long-term consumption of Sumac reduces the cholesterol level.[11] The glycoprotein extracted from the fruit of Sumac also reduces the total cholesterol, triglycerides, LDL-C and increases the antioxidant capacity.[12] Fruit of some other plants such as blueberry which has antioxidant activity causes the dilatation of coronary and systemic arteries, inhibits platelet aggregation and reduces vascular permeability in hypercholesterolemic rabbits[13-16] and may also improve blood flow.[17]

Researches in recent years, other than old markers' role, have considered new markers such as Apo lipoprotein B (Apo B), nitrate, nitrite, fibrinogen and factor VII in the formation of atherosclerosis. High concentrations of some plasma lipoproteins such as VLDL, LDL and IDL are associated with the progression of atherogenesis.[17-21] Lipoproteins containing Apo B-100 have also been known as the carrier of cholesterol into the arterial wall.[22-24] Reports also indicate a relationship between coagulation system components (fibrinogen and factor VII) or fibrinolytic factors (t-PA and PAI-1) and atherosclerosis.[25-27] Fibrinogen is a circulating glycoprotein that works in the stages of coagulating response to vascular and tissue damage. There is a correlation between plasma fibrinogen levels and risk of coronary disease.[23] Despite the thrombosis role, fibrinogen causes vasoconstriction at the injured sites of the vessel wall, stimulation of the platelet aggregation and regulation of cell adhesion.[24-26] Factor VII is a coagulating protein which plays an important role in thrombogenesis. There is a relationship between factor VII and inflammatory parameters (CRP and IL6) in hypercholesterolemic patients, which represent their pathophysiologic relationship in these patients.[27,28]

Although the main mechanism affecting the endothelium consists of several factors, the most important factor is disorder in the eNOS/NO pathway that includes reduction in expression and activity of eNOS and reduction of sensitivity to NO and increased NO destruction by reaction with superoxide. With regard to the expression of eNOS in the vessel wall, eNOS level is reduced in advanced atherosclerosis, which is probably due to the reduced translation or increased eNOS mRNA instability.[27,28] Endothelium-dependent dilation happens in atherosclerotic vessels even before occurrence of any change in the vascular structure and expresses the eNOS reduction. It is known that under certain pathologic conditions such as severe hypercholesterolemia, eNOS is disturbed and nitrite peroxide is produced instead of NO.[27,28]

In view of the side effects of synthetic drugs and individuals' high tendency to the use of herbal medicines and considering the fact that Sumac has antioxidant properties and its long-term intake reduces cholesterol, this study was conducted to determine the effect of consuming Sumac with food on some newly proposed atherosclerosis risk factors (in addition to the old ones) and also liver health indicators (ALT, AST) resulted from high-fat diet stress.

METHODOLOGY

In this study, Sumac was purchased from a local market in Shahrekord and authenticated in herbarium unit of Medical Plants Research Center of Shahrekord University of Medical Sciences. A voucher specimen (no. 268) was deposited there. The Sumac fruit was dried under standard conditions away from sunlight, moisture, microbial contamination with appropriate air-conditioning, and the plant was well powdered by electrical mill, after drying. In order to standardize the powdered Sumac, some factors such as anthocyanins[29] and polyphenols were measured as follows[30]: One gram of powder and 100 ml of ethanol 95% and 1.5 ml normal hydrochloric acid were poured in a 250 ml erlen and covered with Parafilm and kept in refrigerator at 2-4 centigrade degrees for 12 hours. Then, the mixture was filtered and its extract was separated and the residue was repeatedly washed with acidic ethanol solvent, and finally the volume of the solution was brought to 250 ml. Then, its absorption was determined in a one-centimeter cell in the wavelength of 535 nm and its anthocyanin content was measured by the following formula:

A/98.2×25000=The total anthocyanin level (mg per 100 grams of sample).[19]

A=Absorbance sample

Measurement of phenolic compounds: The total amount of phenolic compounds was measured based on Folin-Ciocalteu colorimetric method, equivalent to Gallic acid. At first, standard solutions with concentrations of 12.5, 25, 50, 62.5, 100 and 125 ppm were obtained from Gallic acid in 60% methanol solution. Then 0.1 ml of each was transferred to test tubes and 0.05 ml of 10% reactive solution of Folin-Ciocalteu was added. Then, after

five minutes, 0.4 ml of 7.5% sodium carbonate was added to the solution. The tubes were kept at room temperature for 30 minutes and the absorption level was measured by spectrophotometer for three times at the wavelength of 765 nm. Then, 10 mg of the extract was dissolved in 60% methanol and brought into 10 ml and the level of total phenol content was determined using Folin-Ciocalteu colorimetric method. Then based on the observed uptake, the amount of total phenols was obtained in terms of mg/g of the extract.[30]

Animal experiments: In this experimental study, 24 New Zealand white rabbits weighing 2015±34 grams were bought from Razi Institute, Karaj, Iran. They were acclimated in the animals' nest for two weeks in appropriate temperature and humidity, fed with standard grain food (Razi Co., Karaj). Then, animals were randomly divided into three eight-member groups as follows: normal diet, high-cholesterol diet (1%), high-cholesterol diet with 2% powdered Sumac (2% Sumac powder was added to the rabbit food). In order to provide high-cholesterol diet (1%), one gram of cholesterol (Merck, Germany) was dissolved in 2ml olive oil and was added to regular rabbit food in order to provide 100 grams of high-cholesterol diet. Rabbits of the high-cholesterol diet group and high-cholesterol diet along with intervention (powdered Sumac) were treated with this food. Blood samples were taken from animals in two stages including the beginning of the experiment (after 15 hours of fasting) and three hours after taking the intervention diets.[31,32] At the fasting time, blood samples were collected from the central artery of animals' ear and at the end of the experiment, from the animals' heart. The blood taken from the rabbits was poured into two separate tubes in order to obtain serum and plasma (containing 0.5 cc of sodium citrate). In order to prepare serum and plasma, tubes were centrifuged for 20 minutes with 3500 rpm. Nitrite and nitrate were measured using Griess Reaction method, with the relevant kit (R & D System company, USA), fibrinogen, glucose, total cholesterol, LDL cholesterol, triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and apo lipoprotein B (Apo B) by biochemical kits of the Pars test company using Hitachi 902 auto-analyzer device (Japan) and factor VII by measuring the clotting time in the presence of Neoplastin reagent, with STA-Deficient VII kit, (Diagnostica Stago company, France) using start-4 coagulator device.

Statistical Analysis: To evaluate the biochemical results and compare the test groups, one-way ANOVA and Dunnett post hoc tests were used. The results were calculated as Mean±SE in all cases and $p<0.05$ was considered as significant.

RESULTS

The level of physicochemical parameters measured in Sumac: The amount of anthocyanins in Sumac was 23.7 mg per 100 grams and the amount of its flavonoids and phenolic compounds were respectively 45 and 89 mg per 100grams, equivalent to Gallic acid. The amount of biochemical markers measured in rabbits: The levels of glucose, triglycerides, fibrinogen, LDL-C, TC, AST, and ALT were significantly increased in the high-cholesterol group compared to the normal diet group. Consuming powdered Sumac revealed a significant decrease in blood glucose level compared to the high-cholesterol diet group ($p<0.05$; Table-I). Regarding the lipid profile, consumption of Sumac revealed a significant reduction in LDL-C and cholesterol levels ($p<0.05$) compared to the high-cholesterol diet group. Consuming Sumac did not induce any

Table-I: Values of biochemical factors in experimental groups at the end of trial.

Biochemical factors	*Groups*		
	Normal diet	*High-cholesterol diet*	*Sumac*
Low-density lipoprotein	24.13±1.26*	39.31±3.20	16.44±1.37*
Fibrinogen (mg/dl)	218.9±2.6*	251±4.6	206.1±2.2*
TG (mg/dl)	50.50±1.43*	120.56±5.45	127.33±5
Total cholesterol	56.63±0.68*	91±3.37	63.56±2.07*
Alanine amino-transferase (u/l)	26.63±0.50*	40±1.34	31.78±1.40*
Glucose (mg/dl)	51.25±3.12*	132±3.07	102.33±3.22*
Aspartate amino-transferase (u/l)	29.75±0.53*	43.22±2.62	35.67±1*
Apo-lipoprotein (mg/dl)	27.88±1.42	30.78±1.02	28.89±1.42
Nitrate	305±108.6*	430±36.7	416±65
Nitrite	250.4±10	249.3±10.4	179±50.6
Factor VII	295.7±2.5	298.1±5.7	298.7±5.9

-*$p<0.05$ compared to the high-cholesterol group

significant change on triglycerides (TG) and ApoB ($p>0.05$; Table-I). Consuming Sumac significantly decreased the level of liver enzymes (ALT, AST) ($p<0.05$; Table-I). Considering the inflammatory markers, Sumac consumption significantly reduced the fibrinogen level, but had no effect on factor VII level ($p>0.05$; Table-I).Considering the endothelial markers (nitrite and nitrate), although the amount of nitrite and nitrate was decreased due to consumption of Sumac in comparison with the high-cholesterol diet, the decrease was not statistically significant ($p>0.05$; Table-I).

DISCUSSION

Consuming foods that contain 1% cholesterol increased the total cholesterol, fibrinogen, triglyceride, glucose, nitrate, LDL, liver enzymes ALT and AST, and using powdered Sumac along with high-cholesterol diet revealed a significant decrease in the level of glucose (30.15%), LDL -C (58.17%), total cholesterol (29.5%), ALT (20.55%), AST (17.46%) and fibrinogen (17.92%) compared to the high-cholesterol diet group ($p<0.05$). Research has shown that consumption of high fat foods causes a relatively rapid increase in blood lipids, increased lipid per-oxidation and aggravation of endothelial function destruction which can be blocked by antioxidants.[33] The hypocholesterolemic effects of the Sumac and the effect of the glycoprotein extracted from Sumac fruit in lowering total cholesterol, triglycerides and LDL-C have been previously reported.[11,12]

The present study showed that taking Sumac along with high-fat foods can prevent the transient increase of postprandial blood fat which is highly atherogenic. The level of liver enzymes (ALT, AST) also increased with high fat food intake and decreased with Sumac consumption in this study. The increase in these enzymes following the consumption of high-fat food shows the hepatotoxicity of high-fat foods. The reduction of liver enzymes with Sumac consumption after high-cholesterol meals can show the preventive effect of Sumac against hepatic damage.

Increased cholesterol or triglyceride and decreased HDL concentrations leads to the production of free radicals and oxidative stress accompanied by atherosclerosis aggravation and vascular damage through affecting the Arachidonic acid metabolism and leukocyte stimulation.[34] Increased production of free radicals and oxidative stress reduces the nitric oxide synthesis in endothelial cells. Reduced nitric oxide hurts the endothelium-dependent relaxation of smooth muscles and makes the vessel susceptible to plaque formation.[35]

The direct role of increased free radicals in the development and progression of atherosclerosis proposes the antioxidants as highly effective factors in disease prevention.[36] Phenolic compounds and anthocyanins, whose presence in Sumac was shown in this study, have antioxidant effects and can confront the destructive effects of free radicals caused by consuming high-fat meal. Isoflavones reduce cholesterol levels by increasing the LDL receptors' activity and increasing the LDL catabolism in liver.[37] The presence of isoflavones in Sumac[36] sets forth the possibility of such mechanisms for the effect of this herb. High blood sugar in diabetic patients causes frequent complications such as ocular and vascular diseases. Deposition of collagen and glycoproteins in blood vessel wall causes the vessel wall thickening and consequences resulting from atherosclerosis. Therefore, the hypoglycemic effect of Sumac can be considered as a beneficial factor in reducing atherosclerosis.

Flavonoids existing in Sumac may prevent diabetes complications by hindering the Aldose reductase activity (the enzyme that converts sugar to sugar-alcohol or sorbitol).[38] Flavonoids also inhibit the function of intestinal carriers of glucose and prevent glucose absorption.[39] Another possible mechanism of phenolic compounds is their effects on glucose 6-phosphatase inhibition. The enzyme removes phosphate from esterified glucose. This will lead to glucose release in blood. As a result, the reduction or stopping of the activity of this enzyme will reduce blood sugar.[40] Therefore, blood glucose reduction can be attributed to the flavonoids in the Sumac. Potential mechanism of polyphenols is reducing the digestion absorption of fat and lipase activity in stomach.[41,42] In this regard it has also been reported that Catechin rich polyphenols can significantly inhibit the emulsification and also inhibit the activity of the lipase in pancreas, stomach and duodenum.[43] Impaired fibrinolysis and coagulation is correlated with the progress of cardiovascular diseases such as coronary artery disease, hypertension, and ischemic shock.[44]

Fibrinogen plays an important role in the complication of the atherosclerosis process as a coagulation and inflammatory factor. Fibrinogen oxidation and other residues resulting from fibrinogenase stimulate platelet aggregation and increase IL-6.[45,46] Studies show the effect of herbal diet in the homeostasis of coagulation and fibrinolysis process. These compounds are effective in reducing

the concentration of coagulation factors or increasing fibrinolysis. Some of the herbal compounds are involved in this process through preventing blood from clotting by reducing fibrinogen, increasing fibrinolysis, prothrombin time and inhibiting platelet aggregation. Flavonoids such as quercetin, kaempferol and myricetin are among flavonoids that inhibit platelet aggregation.[47] Polyphenols are rapidly absorbed, which leads to their increased concentration in blood and induction of mRNA expression and fibrinolytic proteins such as t-PA and PAI down regulation.[48] Factor VII activity is correlated with the increased risk of cardiovascular disease. Increased activity of this factor after high fat meal is due to the increased level of VII protein. Factor VII can be acutely set and adjusted by food.

Flavonoids bring about the reduction of coagulation factors such as factor VII.[49] The lack of decrease in factor VII in this research can be due to the short duration of the study, since its synthesis in the liver needs sufficient time. The results of this study showed that Sumac significantly decreases the levels of SGOT and SGPT. The level of these enzymes is increased after a heart attack, liver diseases and diseases that cause muscle damage.[50] Naderi et al.'s studies in 2007 showed that the antioxidant compounds of black pepper lead to reduction of SGPT to 33% in rat liver cells by affecting lipid oxidation in LDL.[51] Therefore, reduction of SGOT and SGPT levels in the high-cholesterol group that received Sumac diet may be due to the antioxidant effects of such plants.Anthocyanins preserve endothelial cells through inhibition of nitrite peroxide that leads to oxidative damage. Anthocyanins act through reducing the expression of iNOS. iNOS is an enzyme produced by different cells by cytokines during inflammatory stress.

It seems that anthocyanins have contradictory effects on Nos isoforms. According to studies, NO production by eNOS has an important role in initiation of coronary arteries' homeostasis, whereas NO production by iNOS can lead to coronary artery diseases. Therefore, anthocyanins play an important role in establishing balance between eNOS and iNOS.[52-55]

CONCLUSION

The results showed that Sumac consumption reduces the risk factors for atherosclerosis. This can be achieved through inhibition of oxidative stress and lipid peroxidation. This study proves the anti-inflammatory and hypolipidemic activity of the Sumac. The hypoglycemic property of Sumac was also confirmed in this study. Since blood glucose is correlated with increased oxidative stress, this effect can also prove the supportive effect of the Sumac.

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Authors Contribution:

YM prepared the primary draft. AM, NS, HN, HSh and MRK wrote some parts of the manuscript. MRK, HN, AB, HSh, NSh and AMP edited the manuscript. MRK prepared the final manuscript.